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NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC) version 6.2020

FDA status: Guardant Health's **Guardant360** plasma-based comprehensive genomic profiling laboratory test has been designated for *Breakthrough Review* by the FDA (and is certified, accredited, or approved by the Clinical Laboratory Improvement Act, College of American Pathologists, and New York State Department of Health, respectively).

On behalf of Guardant Health, I thank the NSCLC Panel and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection. In our common interest in updating these Guidelines, I respectfully request that the Panel consider the following suggestions: (a) name *Guardant360* (as also requested in letters dated January 22 and March 27 of this year); (b) allow clinicians the autonomy to consider *either* tissue- or plasma-based testing, with the latter on the *same footing* as the former, depending on the clinical situation; and (c) clarify "broad molecular profiling." This letter provides a more specific format in line with your requests and cites newly released publications as support.

Page | Topic	Revision *(in blue)*	Rationale
NSCL-18 and NSCL-18A, footnote ii **Plasma or tissue**	***Option A:*** If there is insufficient tissue to allow testing for all of *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET, and RET*~~,~~ results for these biomarkers are not available within 10 days; or tissue biopsy is contraindicated, ~~repeat biopsy and/or~~ plasma testing of cell-free circulating tumor DNA (sometimes referred to as "liquid biopsy"), followed by reflex to repeat tissue biopsy if no circulating tumor DNA alterations are detected, should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes. ***- or -*** ***Option B:*** If ~~there is insufficient tissue to allow testing~~ the result for ~~all~~ any of *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET, and RET* is unknown, plasma testing of cell-free circulating tumor DNA (sometimes referred to as "liquid biopsy") or tissue biopsy (followed by reflex to plasma if no alterations are detected) should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.	This suggestion to make testing for biomarkers treatable with FDA-approved therapies more accessible (by recommending *multiple* methods for genotyping) is supported by the widespread persistence of undertesting or incomplete testing on one hand[1,2,3] and the recent approval of yet more targetable gene treatments (*e.g.*, capmatinib, selpercatinib) on the other. Plasma-based testing through next-generation sequencing (a) is readily accessible and efficient;[4] (b) may be an attractive alternative to more invasive testing, particularly during this time of coronavirus concern; (c) has a quick turnaround;[3] (d) may identify more patients with driver mutations than tissue testing;[3,5] and (e) results in responses similar to those for tissue.[4,6,7,8,9] Well validated plasma-based comprehensive genomic profiling should be recommended on the same footing as tissue-based genomic testing not only upon progression, but *in newly diagnosed patients, regardless of tissue availability or sufficiency*, leaving the utilization of *either* blood or tissue to physicians' discretion (with a recommendation to reflex to tissue if plasma uncovers no driver alterations or to plasma if tissue is insufficient or testing is incomplete).
NSCL-18 and NSCL-18A, footnote kk **Plasma or tissue**	The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling using either cell-free circulating tumor DNA or tumor tissue for comprehensive genomic profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Clinicians may wish to reflex to tissue-based profiling if plasma testing uncovers no known oncogenic driver alterations. ~~Broad molecular~~ Comprehensive genomic profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-H).	

[1] Castellanos, EH, Orlando, A, Ma, X, et al., Evaluating the Impact of Oncology Care Model Reporting Requirements on Biomarker Testing and Treatment. JCO Oncol Pract. 2020 Jun 4. Online ahead of print.
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[3] Leighl, NB, Page, RD, Raymond, VM, et al., Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non–small Cell Lung Cancer. Clin Cancer Res 2019; 25(15):4691-4700.
[4] Mack, PC, Banks, KC, Espenschied, CR, et al., Spectrum of Driver Mutations and Clinical Impact of Circulating Tumor DNA Analysis in Non–Small Cell Lung Cancer: Analysis of Over 8000 Cases. Cancer 2020; 126(14):3219-3228.
[5] Aggarwal, C, Thompson, JC, Black, TA, et al., Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non–Small Cell Lung Cancer. JAMA Oncol 2018; 5(2):173-180.
[6] Reckamp, KL, Patil, T, Kirtane, K, et al., Duration of targeted therapy in advanced non-small cell lung cancer patients identified by circulating tumor DNA analysis. Clin Lung Cancer 2020; Online ahead of print.
[7] Odegaard, JI, Vincent, JJ, Mortimer, S, et al., Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies. Clin Cancer Res 2018; 24(15):3539-3549.
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[9] Paik, PK, Felip, E, Veillon R, et al., Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. N Engl J Med 2020; Online ahead of print.

Page | Topic	Revision *(in blue)*	Rationale
NSCL-G, page 4 of 5 **Plasma or tissue at progression**	For many of the above listed analytes, there is growing recognition of the molecular mechanisms of resistance to therapy. Genomic ~~Re-~~testing of a new sample, acquired through plasma cell-free circulating DNA or tissue biopsy, from a tumor that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps:	Because of *tumor heterogeneity* arising as resistance to targeted therapy develops, testing of a new sample better representing the current tumor environment is more likely to identify resistance mechanisms.[4,10,11]
NSCL-G, page 5 of 5 **Panel size** **Naming of Guardant360**	Studies have demonstrated cell-free tumor DNA testing through comprehensive genomic profiling assays such as Guardant360 or other similarly well validated tests (irrespective of panel size as long as evidence thresholds have been surpassed) to generally have very high specificity~~, but significantly compromised sensitivity, with up to 30% false-negative rate~~ and equivalence to tissue when used to evaluate patients with advanced NSCLC.[3,5] Complete genotyping is critical to maximize treatment benefit while minimizing adverse events.[12,13,14]	NCCN may wish to define "broad molecular" or "comprehensive genomic" profiling *vis-à-vis* "hot-spot" testing, as well as categorize types of testing based upon evidence, classifying specific tests that meet evidence thresholds (*i.e.*, 2A, 2B), with validation and outcomes studies demonstrating utility.[3,4,6,7,9] I understand and respect that NCCN may not routinely recommend specific tests, but suggest that the NSCLC Panel may wish to reconsider naming Guardant360 in *delineating what should and should not be covered*, as many payers and their intermediaries[15,16,17,18] and the NCCN panels for both prostate and breast cancers (in mentioning several RNA expression assays, noting the level of evidence for these assays)[19,20] have done. Oncologists would benefit from clearer guidance on *which tests* are well validated and supported by published studies reporting on clinical utility and outcomes.
NSCL-G, page 5 of 5 **Plasma vs. tissue**	~~Standards for analytical~~ Regarding the performance characteristics of cell-free tumor DNA~~ have not been established~~, ~~and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.~~ a considerable body of evidence demonstrates that response rates to biomarkers detected by plasma are equivalent to those detected by tissue, including for *EGFR*, *EGFR* T790M, *ALK/ROS1*, *RET*, *MET* exon 14, and *BRAF* V600E.[4,6,8]	Although analytic validity standards for liquid biopsy in general may not been established, *some plasma-based assays* (with published clinical outcomes equivalent to those achieved through tissue-based means) *are acceptable*.[4,6,7,8,9] Oncologists would benefit from direction as to *which tests* are supported by published data pertaining to clinical utility and outcomes.
NSCL-G, page 5 of 5 **Indications for cell-free DNA**	The use of cell-free/circulating tumor DNA testing ~~can~~ should be strongly considered in ~~specific clinical circumstances~~ any setting in which data from compete biomarker testing are lacking and adequate tumor tissue for analysis is not in hand, most notably: ◊ If a patient is medically unfit for invasive tissue sampling ◊ In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis~~, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which~~ and an oncogenic driver ~~is~~ has not been identified ◊ If a patient is progressing, and testing for *EGFR, EGFR* T790M, *ALK/ROS1*, *RET*, *MET* exon 14, or *BRAF* V600E was not completed at diagnosis[4,11] ◊ If a patient is progressing, and testing may identify a treatable resistance mechanism or targeted therapy[4,11]	The NSCLC Panel can meaningfully address the prevalent problem of *undertesting*[1,2,3] and associated *deprivation of targetable treatments* by supporting plasma-based in addition to tissue-based testing, as the former (a) is more readily accessible and efficient;[4] (b) may be more attractive as a less invasive means, particularly in times of pandemic; (c) has a quicker turnaround;[3] (d) may identify more patients with driver mutations;[3,4,5,11] and (e) results in similar responses.[4,6,7,8,9]

Thank you for considering these suggestions to address the challenges of undertesting and underutilization of targeted therapy through greater access to well validated plasma-based comprehensive genomic profiling.

Sincerely,

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[12] Schoenfeld, AJ, Arbour, KC, Rizvi, H, et al., Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. Ann Oncol 2019; 30(5):839-844.
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[15] Palmetto GBA Medicare Administrative Contractor, "Local Coverage Determination (LCD): MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043)," effective March 5, 2020.
[16] Blue Shield of California, "Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy)," effective March 1, 2020.
[17] Evidence Street, BlueCross BlueShield Association, "Circulating Tumor DNA Management of Non-Small Cell Lung Cancer (Liquid Biopsy)," effective November 2019.
[18] eviCore healthcare, "Clinical Guidelines: Lab Management Program," effective July 1, 2019.
[19] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Prostate Cancer, Version 2.2020 – May 21, 2020, page PROS-2A.
[20] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Breast Cancer, Version 4.2020 – May 8, 2020, page BINV-N 1 of 4.